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SOCIETY OF MEDICAL OFFICERS OF HEALTH.

FEVER HOSPITALS MEDICAL SERVICE GROUP.

AT the annual meeting of this group, held at the Society's house in London on May 22nd, a discussion took place on the

DICK REACTION AND THE SERUM TREATMENT OF SCARLET FEVER.

Dr. E. W. GOODALL (N.W. Fever Hospital, Metropolitan Asylums Board), Vice-President, occupied the chair.

Dr. R. A. O'BRIEN (Wellcome Physiological Research Laboratories), in opening the discussion, said :—

I should like to give some short account of what progress has been made in England in the application of the results obtained in America, notably by the Dicks, Dochez, Park and Zingher. But I would prefer to draw your attention at greater length to the difficulties ahead and the urgent problems awaiting solution before much progress can be made.

Progress in England.

Dick Test.—The results obtained in England, such as the series published by Okell and Parish in July, 1924, and April, 1925, and the longer series by Ker (THE LANCET, 1925, i., 230), as well as a number of shorter series by various observers (over 200 cases, 70 per cent. being positive to the Dick reaction) agree in the main with American findings. Some 60 per cent. to 90 per cent. of cases of scarlet fever if tested during the first two or three days of the disease give a positive response. If tested two to five weeks after the onset of the disease some 70 per cent. to 90 per cent. of patients have developed a sufficient immunity to give a negative reaction to the Dick test (100 cases, 89 per cent. negative).

Schultz-Charlton Test.—Although the observations made in England up to the present are few in number, the results agree broadly with the American findings. The serum of a patient taken some weeks or more after the end of the disease will, when injected intradermally into the rash of a scarlet fever patient within 60 hours of its appearance, blanch an area of from 10 to 40 mm. ; this blanching appears in from 6 to 12 hours and lasts usually from 24 to 48 hours. We have immunised several horses with toxin and streptococci, and the serum of these horses when injected intradermally also causes the characteristic blanching in rashes due to scarlet fever but not in rashes due to other diseases. In England this blanching has been obtained in some 70 per cent. of over 100 cases tested.

Active Immunisation.—Apparently very little work has been done in England. We have injected many minimal skin doses into ourselves without producing any troublesome reaction.

Passive Immunisation.—Apparently 5 to 10 c.cm. of our horse serum injected intramuscularly will convert a " positive reactor " into a " negative " overnight. The serum should therefore efficiently protect children unwittingly exposed to infection.

Treatment.—The serum of several horses has been used therapeutically in some few dozen cases. The results can be characterised broadly as promising, and in some instances as very promising. The number is far too small to enable one to draw any satisfactory conclusions, but the evidence is such as to lead us to commence the immunisation of a larger number of horses so that sufficiently large supplies of serum will be available for a test carried on over many months.

Difficulties and Discrepancies.

The foregoing is a short account of what has been done. I should now like to deal with the difficulties and discrepancies.

Dick Test.—Here, as in all the work, we are greatly hampered since there is no means yet discovered of testing a given toxin in the laboratory. When we speak of the Schick test we can be certain that results obtained in half a dozen different countries are reasonably comparable, but with the Dick test this cannot be so readily assumed. There is little doubt that if an accurate method of titration were discovered it would be found that some of the Dick toxins in use for the test in various localities are two or more times the strength of those used elsewhere. We have tried all the obvious animals as well as white goats and kids and grey horses, cow's udder, abdomen of white sucking pig, the axilla of white sheep and lambs, but can find no practical method of testing in the laboratory. All toxins, therefore, must be tested on human beings. We have injected ourselves in the laboratory many times until we no longer give a satisfactory positive reaction. In America and France large numbers of people are available, but in England unfortunately they are not. How the difficulty is to be solved I do not know. It is a very serious one. Here, perhaps, I may be allowed to express the deep appreciation of myself and colleagues for the unlimited and prompt generosity of the whole of the American workers in putting at our disposal information and materials. We have tried to compare our toxins with those in use in America, but I know from American experience that a toxin may easily be labelled with half or double its real value when tested on a small number of people. So far as we can determine, the filtrates Dr. Okell has made are at least as strong and probably stronger than the average American toxins, and seem to cause fewer pseudo-reactions. At present we must go on collecting the observations made by a small number of medical officers and be prepared to alter our view about any given toxin whenever the evidence indicates. We have found recently an indication that a toxin with which Dr. Okell gets quite satisfactory positive reactions in the laboratory is giving a very low percentage of positive reactions in certain hospitals, mostly when testing patients in the first few days of scarlet fever, but also on patients not suffering from scarlet fever. It may be that transient positive reactions are being missed. It is puzzling that, during the same period, with the same toxin dilution from the same stock, satisfactory positive reactions are being got in other hospitals. It may be that it will be found necessary to use a given strength of toxin for testing healthy normal subjects, and a toxin several times as strong for testing scarlet fever patients in the first few days of the disease. Such a course would lead to great confusion and difficulty in keeping records, and one can only hope that it will not be found to be necessary. At present we have two dilutions being tested clinically, 1/6000 and 1/1000.

Schultz-Charlton Test.—We are naturally mainly interested in the blanching produced by the serum of immunised horses. In this test the American and Continental workers inject into the skin 0·5 to 1 c.cm.

of serum. We are using 0·2 c.cm. The injection is much less troublesome for the patient and apparently gives satisfactory results, but we have not had enough experience to say which is the best quantity to use. Apparently some 75 or 80 per cent. of cases give an easily recognised blanching whether the serum be used undiluted or diluted even 200 to 500 times, but it is curious that in most if not all of the series done in England a small number of the patients suffering from typical scarlet fever have failed to show any blanching, though the serum has been injected intradermally in the very early stage of the disease. The most obvious suggestion is that there are two types of scarlet fever—A and B. It would be easy in a comparatively short time to confirm or refute this hypothesis. My own feeling is that it will not be confirmed, but evidence to-day is too slight to warrant anything more than a guess. We are collecting the streptococci from these "non-blanching" patients, and making toxin to see if one can demonstrate any difference from the ordinary toxin. If the result of the Dick and Schultz-Charlton test in these patients is known, and also the effect of their serum (taken when convalescent) in producing the blanching on other cases of scarlet fever, it will be easy in a relatively short time to decide the question.

Active Immunisation.—We have made toxin for active immunisation, and Dr. Okell has formalinised some toxin by the Glenny-Hopkins technique, but we have no group of people available on whom to test the immunising efficiency of these toxins. The results obtained recently in America already almost justify the conclusion that by testing and immunising the ward staffs in scarlet fever hospitals we can reduce attacks of scarlet fever amongst nursing staffs as satisfactorily as now, in many diphtheria wards, diphtheria amongst the nursing staff has been reduced almost to nothing. One point of importance here is that in the process of immunisation there is but little danger. In diphtheria a careless miscalculation has in rare cases caused diphtheritic paralysis or death, whereas the injection of very large doses of scarlet fever toxin into human patients has been followed by nothing more than a feverish attack lasting 24 to 72 hours with complete recovery thereafter. There need apparently be no hesitation in arranging for the immunisation of suitable people.

Treatment.—The results hitherto obtained are encouraging ; it is too early to say more yet. But the great difficulty that faces us here is that of standardisation. There are two possible methods—the official U.S.A. method and the rash-blanching method.

Official U.S.A. Method.—In principle this method resembles the titration of diphtheria antitoxin by the intradermal method in guinea-pigs. Mixtures are made each containing a fixed dose of toxin and a dilution of the serum under test ; the various mixtures are injected intradermically. If a flush—i.e., a positive reaction—occurs, obviously more serum must be used. This is continued until a balance is reached. So far as our experience of tests carried out on ourselves goes, the process is reasonably satisfactory and enables one to get an idea of the value of a serum. This value, of course, is much less accurate than in the case of diphtheria antitoxin, but still serves as a valuable measure of potency when arranging for the treatment of human beings. The only trouble is the obtaining of a supply of Dick positive people on whom to carry out the tests. The process of testing is practically painless and apparently free of danger, so that when suitable opportunity occurs there need be but little hesitation in carrying out the test. which is also a test of the patient's immunity to scarlet fever. The tendency of a number of tests would be to immunise the patient against scarlet fever after which, of course, he would be useless for this method of test. The second method is the one that is being used in England in which the serum is tested intradermally on scarlet fever patients before its therapeutic use. Into the rash is injected 0·2 c.cm. of dilutions of the serum proposed for use until the greatest dilution which will still produce blanching is found. We have compared our own horse serum with samples very kindly sent us from American colleagues; the serum in use in England will usually blanch in a dilution of 1/200 or even 1/500. The number of comparisons yet made is very small, but they tend to show that our serum has a value at least equal to the American serum. This method of testing appears to be more practicable under English conditions. Unfortunately, no one can as yet tell us definitely whether this method gives the same relative values as the official U.S.A. method. Until this problem of standardisation is solved no great improvement in the potency of the serum available can occur. We are using for the immunisation of horses the filtered toxin and the cocci themselves. We have applied the ordinary methods of concentration on a small scale to this serum, but we have not up to the present been able to form any idea whether a concentration of the scarlet fever antitoxin does result. I have little doubt that it does, for concentration has been used on a fairly large scale in America, but so far as our own work is concerned we are still without definite information.

Discussion.

Dr. C. C. OKELL (Wellcome Physiological Research Laboratories) said that with regard to the standardisation of the Dick toxin there was great difficulty in matching two toxins. They had made filtrates not only from the Dochez strain but from the Dick strain, and from one or two strains of their own, but outside work had been restricted to the Dochez toxin. The toxins were not all of the same strength, but could be made so by suitable dilution, and it could probably be claimed that the Dick tests being carried out in the several countries were the same. Doubtless everybody wanted to know what was the correct dose—the dose that would divide patients accurately into two groups, those who would get scarlet fever and those who would not. That point had not yet been settled, and only much experience would provide the answer. Evidence, of course, was rapidly accumulating which showed that the Dick negative did not take scarlet fever, but light still had to be thrown on the meaning of the partial reactions, and whether or not the people who gave them were susceptible to scarlet fever. Dr. Okell instanced several specific cases of positive reactions, including that of a nurse, the only Dick positive in a group, who before she could be got out of the ward developed scarlet fever. One thing might help to clear up certain difficulties—viz., the study of the disease with a serial Dick test day after day during its course. Such a test done in parallel with the Schultz-Charlton would give valuable information.

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